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BUCHANAN, INGERSOLL & ROONEY PC
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HOLT, ANDRIAE M	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/031,949
Filing Date: May 01, 2002
Appellant(s): COUARAZE ET AL.

Brian P. O'Shaughnessy
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 5, 2010 appealing from the Office action mailed December 7, 2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Pending claims 3-6 and 8-18 are finally rejected.

(4) Status of Amendments After Final

The appellant's statement of the status of the amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

4,684,516	Bhutani	08-1987
4,806,361	Harrison et al.	02-1989
WO 88/02629	Frost et al.	02-1988
5,026,560	Makino et al.	06-1991

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Bhutani (US 4,684,516).

Bhutani discloses the active ingredient is first coated onto non-pareil beads (neutral microgranules, 62.5% to 91.5% sucrose and the remainder starch) or onto drug crystals or granules. Bhutani discloses these pellets are then divided into several groups and varying amounts of retarding materials are applied to different groups. Bhutani discloses the stabilized pellets are then coated with several layers of disintegrating agent or agents (active agents) and compressed into tablets or pills, after adding a small amount of lubricants or other inert ingredients, if necessary (lubricant of 0 and 1%)(tableting premix). Bhutani discloses that such a compressed tablet, when tested in water or gastric fluid, breaks up quickly thereby releasing the individual pellets in a matter of minutes, whereupon they act as independent pellets releasing their medicine at a predetermined rate (col. 4, lines 11-29). Bhutani teaches the tablet is composed of 85% to 98% of the drug-containing, coated, spherical pellets, the remainder being composed of binder and lubricants, preferably between 90% to 100% of the tablet (99 and 100% neutral microgranules). The pellets are predominantly of a size ranging from 12 to 30 mesh, with sizes 16 thru 24 mesh being preferred and they all may be the same size or of different sizes within that range (col. 5, lines 40-47). The 12 to 30 mesh is within the same range as 200 and 400 μm of the instant invention. Bhutani discloses in examples 1, 3, and 4 preparation of tablets using Nonpareil seeds (sugar pellets). Bhutani disclosed in example No. 4, Nonpareil seed (sugar pellets), 30.0

kg., all passing through a No. 30 U.S. mesh screen, 90% passing through a No. 35 U.S. mesh screen, and not over 10% passing through a No. 40 U.S. mesh screen are placed in a 48-inch coating pan. The pan is set in rotation and coating solution is sprayed slowly onto the pellets in order to wet them evenly. Then 400 gm of theophylline anhydrous containing approximately 5% talcum powder is sprinkled on the wetted mass of nonpareil seeds.

These tablets are then coated using conventional coating techniques for improving appearance and acceptability. The coated tablets thus obtained released the active ingredient at a sustained rate over a period of 10 to 12 hours under physiological conditions (col. 11, lines 1-49).

Bhutani meets all the limitations of the claims and thereby anticipates the claims.

Claims 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Harrison et al. (US 4,806,361).

Harrison et al. disclose in col. 6, lines 29-47, the preparation of Nonpareils Coated with Medicament. Harrison et al. disclose that 11 parts of hydroxypropylmethylcellulose were suspended in 111 parts of purified water previously heated to boiling. 440 additional parts of water were then added to the suspension and the whole stirred until a diluted Pharmacoat suspension had formed. Harrison et al. further disclose that 11 parts of 1,2 dihydro-3-cyano-6-methyl-5-(4-pyridinyl)-2(1H)-pyridinone (active agent) were stirred into the Pharmacoat suspension until well dispersed. 200 parts of nonpareils (sugar/starch base: 25-30 mesh) (neutral

microgranules) were placed in a coating column or pan and, whilst passing an atomizing current of warm air there through, the diluted Pharmacoat suspension was gradually added. Harrison et al disclose that after all the Pharmacoat suspension had been added, the passage of the current of warm air was continued until the coated nonpareils were dry.

Harrison et al. meet all the limitations of the claims and thereby anticipate the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-6 and 8-18 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Frost et al. (WO 88/02629) in view of Makino et al. (US 5,026,560).

Applicant's Invention

Applicant claims a tablet comprising less than 40 mg/g of active principle attached as a coating to neutral microgranules comprising 62.5 to 91.5 % sucrose and

the remainder starch. Applicant claims the tablet includes a compression excipient at less than 1% by weight of the tablet.

Determination of the scope of the content of the prior art (MPEP 2141.01)

Frost et al. teach on page 4, example II, alcohol dissolved Killodone 90 is used as a wetting agent for nonpareil seeds (20 to 30 mesh) in a coating pan with repeated dustings of 2', 3'-didesoxyadenosine (about ten to twenty times) to build up a 2', 3'-didesoxyadenosine-coated nonpareil seed. Frost et al. teach a total adult daily dosage is spread out over three to five administrations per day, or twice daily in the sustained release. Frost et al. teach the tablets comprise from about 2 to about 1000 mg per day, most preferably 10 to 250 mg per administration (page 4, lines 13-18) (40 mg/g active). Frost et al. teach in one embodiment there is a sustained release composition which comprises a plurality of dosage units each having at least two components including 2', 3'-didesoxyadenosine and an outer inert component stable in acidic pH which dissolves in a basic pH. Frost et al. teach tablets of a total weight of 330 mg are produced by mixing and then compressing together in a ratio of 10:1 of the dosage subunits of example II and hydroxypropylmethyl cellulose. Frost et al. teach the sustained release tablet of example VII provides an advantage over the other dosage forms in that the dosage subunits are only gradually exposed to the environment of the gastrointestinal fluids, whereby 2',3'-didesoxyadenosine is introduced into the bloodstream over a prolonged period of time (page 6, lines 3-12). Frost et al. teach the compressed tablet

containing the plurality of dosage subunits, the matrix of the tablet disintegrating in the gastrointestinal tract to yield the plurality of dosage subunits (page 2, lines 11-15).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Frost et al. do not teach the compression force between 10 and 30 kN or the disintegration is less than 15 minutes. It is for this reason Makino et al. is joined as a secondary reference.

Makino et al. teaches spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose, because of their excellent hardness, can be coated further evenly, (e.g. sustained release coating, gastric coating, enteric coating), and at the time the granules are excellent in disintegration(Abstract). Makino et al. teach seed cores include Nonpareil produced by coating sucrose (75 weight parts) with corn starch (25 weight parts) according to the per se known method, and spherical seed cores using crystalline cellulose. Makino teaches the particle size of the said seed cores is generally 14-80 mesh (col. 3, lines 30-35). Makino et al. teach the spherical granules having a core may be coated according to the per se known method for the purpose of taste masking, enteric coating, gastric coating, or prolongation, (col. 4, lines 15-19) (film coating). Experimental example 1 in col. 8, lines 20-50, teach the disintegration times and hardness of the various excipients used in the production of the granules. The disintegration ranges from 1 minute to 30 minutes.

Finding of prima facie obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Frost et al. and Makino et al. and produce tablets that have a disintegration rate less than 15 minutes. One skilled in the art at the time the invention was made would have been motivated to have a disintegration rate less than 15 minutes because Frost et al. teach granules disintegrate rapidly in the gastrointestinal fluids. In addition, Makino et al. teach that the use of certain excipients and binders, some of which are the same binders that may be incorporated in the matrix taught by Frost et al., have disintegration times ranging from 1 to 30 minutes, the median of which is 15 minutes.

Each of the references is silent as to the compression force ranging between 10 and 30 kN. However the adjustment of the compression force is a matter of routine experimentation and optimization to produce the tablets. One skilled in the art at the time the invention was made would have been motivated to adjust the compression force to range between 10 and 30 kN to produce a tablet with good hardness. The adjustment of particular conventional working conditions (e.g., compression force) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. Accordingly, this type of modification would have been well within the purview of the skilled artisan and no more than an effort to optimize results.

Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited references.

(10) Response to Argument

Appellant argues that Bhutani describes high dose formulations that are fundamentally different than the claimed invention. Appellant further argues that Bhutani describes a controlled release pharmaceutical formulation wherein an active is coated on non-pareil beads and the resulting pellets are coated with varying amounts of retarding material. This argument is not persuasive because Bhutani discloses a premix formulation that is composed of 85% to 98% of the drug containing, coated, spherical pellets. Bhutani discloses in example 4 that the theophylline anhydrous containing approximately 5% talcum powder was sprinkled on the wetted mass of nonpareil seeds. The talcum powder is used as a binder in the formulation. Appellant claims a "tableting premix" wherein the neutral microgranules are coated with an active principle and "the active principle mixture consists essentially of an active principle and an optional binder". As such, the skilled artisan would anticipate that the pellet composition as taught by Bhutani would anticipate the instant claims, especially since Appellant does not indicate the amount of binder that can be used in the formulations. Bhutani discloses more coatings of the theophylline anhydrous coating containing the talcum powder are applied to the nonpareil seed until the theophylline anhydrous powder is used up. Appellant does not indicate that only one coating of the active principle mixture is applied to the neutral microgranules. The nonpareil seed pellets coated with the

active agent taught by Bhutani anticipates the premix of the instant application in that no lubricant is used in the formulation.

It is maintained that the reference cited anticipates the instant claims obvious.

Appellant argues that Harrison et al. disclose that the active agent-coated beads are further coated with a “sustaining coating” comprising at least three polymers. Appellant argues that Harrison et al. does not teach how to make formulations that exclude those elements, much less formulations that can be directly compressed into stable, durable tablets. This argument is not persuasive because Appellant's independent claim 11 that stands rejected is drawn to a “tableting premix" that is compressible. Harrison teaches in Preparation A, the 1,2 dihydro-3-cyano-6-methyl-5-(4-pyridinyl)-2(1H)-pyridinone (active agent) were stirred into the Pharmacoat. Pharmacoat is used in the formulation as an adhesive, a binder. Appellant claims a “tableting premix” wherein the neutral microgranules are coated with an active principle and “the active principle mixture consists essentially of an active principle and an optional binder”. As such, the skilled artisan would anticipate that Preparation A as taught by Harrison would anticipate the instant claims, especially since Appellant does not indicate the amount of binder that can be used in the formulations. Harrison does disclose that the Pharmacoat suspension was gradually added until all the Pharmacoat suspension had been added, but does not indicate it was added in layers. In addition, Appellant does not indicate only one coating of the active principle mixture is applied to the neutral microgranules. The Preparation of the Nonpareils Coated with Medicament

taught by Harrison anticipates the premix of the instant application in that no lubricant is used in the formulation.

It is maintained that the reference cited anticipates the instant claims.

Appellant argues Frost et al. teach away from the claimed formulation because it requires substantial additional ingredients. Appellant argues that it cannot be argued that hydroxypropylmethylcellulose of Frost et al. can be equated with the optional binder because in the instant claims the binder must be included in the pre-mix or active principle. Appellant argues that Frost et al. teach the use of hydroxypropylmethyl cellulose at 10% of the composition, which is more than the 1% claimed. Appellant argues that the teachings of Makino et al. do not remedy the deficiencies of Frost et al. This argument is not persuasive because Frost et al. teach in example II, page 4 formulations of nonpareil seeds coated with 2', 3'-didesoxyadenosine. The formulation taught in example 4 is equivalent to Appellant's premix formulation that does not require substantial additional ingredients. The subunits of example II, the premix formulation, and hydroxypropylmethylcellulose (excipient) are compressed together to form a tablet at a weight ratio of 10:1. If the weight ratio is 10:1 then it would have been obvious to the skilled artisan that small amounts of hydroxypropylmethylcellulose could be used in the formulation, including a weight of 1%, as a matter of routine optimization. Hydroxypropylmethylcellulose is a known excipient in the pharmaceutical art. It would have been obvious to the skilled artisan to vary the amount of excipient used in the

formulation to produce a tablet formulation that has the properties that are desired in the formulations.

In response to Appellant's argument that Makino et al. do not remedy the deficiencies of Frost et al., Makino et al. was relied on to teach disintegration is less than 15 minutes. One skilled in the art at the time the invention was made would have been motivated to have a disintegration rate less than 15 minutes because Frost et al. teach granules disintegrate rapidly in the gastrointestinal fluids. In addition, Makino et al. teach the use of certain excipients and binders, , i.e., hydroxymethypropylcellulose, are formulated with the granules have disintegration times ranging from 1 to 30 minutes, the median of which is 15 minutes. Hydroxymethylpropylcellulose is the same excipient used in the formulation taught by Frost et al. As such, it would have been obvious to the skilled artisan that since the same binders and excipients, which control disintegration rates, were used in the prior art references, the disintegration times of the Frost formulations would fall within the range of 1 to 30 minutes, the median of which is 15 minutes.

It is maintained that the combination of the references cited render the instant claims obvious.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616

Conferees:

/Andriae M. Holt/

Patent Examiner, Art Unit 1616

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627